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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BARNHART, LORA ELIZABETH	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/730,549	LAUGHLIN ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,10-12,21-43,48,50-54,56,57,62,63 and 67-69* is/are pending in the application.

4a) Of the above claim(s) *5,9,22,37-39,48,50-53,62 and 63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,10-12,21,23-36,40-43,54,56,57 and 67-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/19/10 has been entered.

Response to Amendments

Applicant's amendments filed 3/19/10 to claims 1, 24-26, 29, 31-33, 54, and 57 have been entered. Claims 64-66 have been canceled. No claims have been added. Claims 1, 2, 4, 5, 10-12, 21-43, 48, 50-54, 56, 57, 62, 63, and 67-69 remain pending in the current application, of which claims 1, 2, 4, 10-12, 21, 23-36, 40-43, 54, 56, 57, and 67-69 are being considered on their merits. Claims 5, 9, 22, 37-39, 48, 50-53, 62, and 63 remain withdrawn from consideration at this time. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Applicant's reply refers to the patentability of claims "62-69," *inter alia*, as well as "new claims 70 and 71." However, the claim listing submitted 3/19/10 cancels claims 64-66 and does not add any new claims. The claims as described above are pending and under consideration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 10-12, 21, 23-36, 40-43, 54, 56, 57, and 67-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strauer et al. (2002, *Circulation* 106: 1913-1918) taken in view of Shake et al. (2002, *Annals of Thoracic Surgery* 73: 1919-1926), Ueno et al. (U.S. Patent Application Publication 2002/0037278), Kawamoto et al. (2001, *Circulation* 103: 634-637; reference CJJ on 11/13/06 IDS), Itescu (2003, U.S. Patent Application Publication 2003/0199464), and Peichev et al. (2000, *Blood* 95: 952-958; reference CZZZ on 4/26/06 IDS).

Strauer et al. teach isolating bone marrow (BM) from humans (page 1914, column 1, paragraph 5); isolating bone marrow mononuclear cells (BMCs) therefrom; cultivating them overnight in a buffered tissue culture medium comprising autologous serum (page 1914, column 2, paragraph 1), and administering over 10^6 BM-MNCs to the ischemic tissue using a balloon catheter, specifically via intracoronary administration

at ischemic myocardium in a subject in need thereof (page 1914, column 2, paragraph 2; page 1915, column 2, paragraph 3). Strauer et al. teach administering between $1.5x10^6$ and $4x10^6$ BM-MNCs 6 or 7 times, *i.e.*, between $9x10^6$ and $2.8x10^7$ BM-MNCs; Strauer et al. also teach that 0.65% of BM-MNCs are $AC133^+$ ($CD133^+$). Therefore, Strauer et al. teach administering between $5.9x10^4$ and $1.8x10^5$ $AC133^+$ EPCs. Strauer et al. teach that said injections resulted in improved cardiac function, cardiac geometry, and contractility (page 1915, column 2). Strauer et al. teach that their BMCs comprise mesenchymal stem cells (MSCs) as well as endothelial progenitor cells (EPCs; page 1916, column 2, paragraph 2).

Strauer et al. do not teach administering a population of cells comprising at least 75% $CD34^+CD133^+$ EPCs. Strauer et al. do not teach administering cells in the ratios recited in claims 28, 53, 67, and 68. Strauer et al. do not teach all of the modes of administration recited in claims 29-32. Strauer et al. do not teach coadministering the cells with VEGF or any recombinant polypeptide, as in claims 40-43. Strauer et al. do not teach administering allogeneic EPCs.

Shake et al. teach isolating MSCs from bone marrow and culturing them such that hematopoietic cells, fibroblasts, and non-MSC adherent cells are washed away, yielding a purified MSC culture (page 1919, column 2, through page 1920, column 1). Shake et al. teach administering said MSCs directly to an infarcted region of heart tissue in recipient pigs (page 1920, column 2). Shake et al. teach that MSCs so administered engraft into the host myocardium, express muscle-specific proteins, and

have a beneficial impact on cardiac remodeling after myocardial infarction (page 1923, column 1).

Ueno et al. teach methods for treating ischemic tissues by administering bone marrow mononuclear cells; Ueno et al. teach that the administration may be local or systemic and may be carried out via injection or infusion into arteries or veins, directly into an occlusion, or application into a tissue or organ of interest (paragraphs 0034 and 0035). Ueno et al. teach that large amounts of cells may be administered to patients safely (paragraph 0037) and that the number of cells administered is optimizable (paragraph 0034). Ueno et al. teach coadministering recombinant VEGF with the BMCs (paragraph 0042).

Kawamoto teaches administering expanded endothelial progenitor cells (EPCs) to rats in which myocardial ischemia has been induced. See pages 634-635. Kawamoto teaches that EPCs so administered promote neovascularization. See pages 636-637.

Itescu teaches methods for regenerating myocardial tissue after ischemic damage by promoting neovascularization with an injection of endothelial progenitor cells (paragraph 0055). The EPCs of Itescu are found in bone marrow (paragraph 0056), express CD34 and CD133 (paragraph 0061), and may be allogeneic with respect to the recipient (paragraph 0057). Itescu teaches that the number of cells administered to the patient may vary (paragraph 0056), as may the location of the injection (paragraph 0061).

Peichev teaches methods for purifying CD34+ CD133+ cells using fluorescence sorting (Figure 2A; Figure 3C). Peichev teaches that AC33 and CD34 are markers of epithelial endothelial progenitor cells (EPCs) (page 955). Peichev teaches that ventricular neo-intima is populated *in vivo* with cells that express CD34 and CD133 (page 956, column 1, and Figure 6).

The independent claims have been amended to include the transitional phrase "consisting essentially of." M.P.E.P. § 2111.03 clearly indicates that "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original). "A 'consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a 'comprising' format." *PPG Industries v. Guardian Industries*, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998), *et al.* For the purposes of searching for and applying prior art under 35 U.S.C. §§ 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. *In re De Lajarte*, 337 F.2d 870, 143 USPQ 256 (CCPA 1964) *et al.* Since the specification in this case does not particularly point out the

basic and novel characteristics of the claimed composition, the phrase “consisting essentially of” in claims 1, 24, 54, and 57 has been interpreted as “comprising” for the purpose of art rejections.

A person of ordinary skill in the art would have had a reasonable expectation of success in enriching the $CD34^{+}CD133^{+}$ EPCs within the BM-MNCs of Strauer et al. at least twofold because Peichev et al. teach methods for enriching such cells using fluorescence sorting. The skilled artisan would have been motivated to enrich the $CD34^{+}CD133^{+}$ EPCs in the administered composition of Strauer et al. because Kawamoto et al. recognized that EPCs promote neovascularization of ischemic tissue; therefore, administering more cells known at the time of the invention to achieve the desired result of Strauer et al. would improve the outcome of the method of Strauer et al.

The person of ordinary skill in the art would have had a further reasonable expectation of success in coadministering the EPCs of Strauer et al. with the purified MSCs of Shake et al. because the cited references teach that both cells promote healing after myocardial infarction. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted). See M.P.E.P. § 2144.06. Since Shake et al. teach that their MSCs are “purified” after their culturing step, the level of enrichment would have been a matter of

routine optimization at the time of the invention, the skilled artisan recognizing that Shake et al. identified a property of MSCs (i.e., cardiac remodeling) and that it would have been desirable to administer as many cells with that property as possible in treating myocardial infarction.

The person of ordinary skill in the art would have had a further reasonable expectation of success in coadministering the VEGF of Ueno et al. with the cells of Strauer et al. and Shake et al. in the method of Strauer et al. because Ueno et al. teach methods for administering recombinant polypeptides and that such polypeptides may be coadministered with cells. The skilled artisan would have been motivated to include VEGF with the stem cells in the method of Strauer et al. in view of Shake et al. because Ueno et al. teach that VEGF is a growth factor that promotes neovascularization upon administration to a patient.

The person of ordinary skill in the art would have had a further reasonable expectation of success in administering allogeneic cells in the method of Strauer et al. in view of Shake et al. because Itescu teaches that allogeneic EPCs promote neovascularization. The skilled artisan would have been motivated to administer allogeneic EPCs in the method of Strauer et al. in view of Shake et al. for the expected benefit that the pool of donor cells would be dramatically increased in size.

The selection of the mode of administration of the cells in the method of Strauer et al. in view of Shake et al. would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Ueno et al. and Itescu both teach that ischemia may be treated bone marrow-derived cells administered in any

of a variety of means. A holding of obviousness over the cited claims is therefore clearly required.

The selection of the number of each type of cell to administer in the method of Strauer et al. in view of Shake et al. would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Strauer et al., Shake et al., Ueno et al., and Itescu all teach that these numbers may be modified depending on the desired outcome. A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to enrich the $CD34^+CD133^+$ EPCs from the BM-MNCs of Strauer et al. using the methods of Peichev et al. and administer more such $CD34^+CD133^+$ EPCs with the purified mesenchymal stem cells of Shake et al. in the method of Strauer et al. because Kawamoto et al. and Shake et al. teach that EPCs and MSCs, respectively, promote neovascularization, and Peichev teaches that EPCs express CD34 and CD133. It would have been further obvious to coadminister recombinant VEGF with the cells in the method of Strauer et al. in view of Shake et al. because Ueno et al. teach that VEGF is a growth factor that promotes neovascularization and aids in treating ischemia. It would have been further obvious to administer allogeneic EPCs in the method of Strauer et al. in view of Shake et al. because Itescu teaches that allogeneic EPCs promote neovascularization. Finally, it would have been further obvious to vary the numbers of each type of cell administered

and the mode of administration because Strauer et al., Shake et al., Ueno et al., and Itescu concur that these are optimizable variables for the reasons discussed above.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicants allege that Strauer does not teach administering a composition comprising 75% CD133+/CD34+ cells. See reply, page 13. Applicants allege that the art does not teach that EPCs promote neovascularization in ischemic tissue. See reply, page 15. Applicants allege that none of the other references teaches the claimed coadministration. See reply, pages 13-16. Applicants allege that Strauer teaches away from the claimed invention by indicating that BM-MNC alone can perform the claimed function. See reply, page 17. These arguments have been fully considered, but they are not persuasive.

Applicants' concerns about the obviousness of purifying CD133+ CD34+ cells to yield a composition comprising at 75% such cells are addressed by the Peichev reference. Applicants' concerns about the ability of EPCs to promote neovascularization in ischemic tissue are addressed by the Kawamoto reference.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The rejection is based on the fact that at the time of the invention, MSCs and EPCs were both recognized in the art for treating ischemic tissue, and the art also

taught methods for purifying, enriching, and administering these cells. When all of the references are considered together, the claimed invention is obvious.

Applicant's comments at page 17 misrepresent Strauer's teachings. Strauer recognized that whole BM-MNC has "large and perhaps heterogeneous regenerative potential" and decided to maximize that potential by administering whole BM-MNC. Shake teaches that MSCs, a component of BM-MNC, treat ischemic tissue. Kawamoto teaches that EPCs, another component of BM-MNC, treat ischemic tissue. Strauer's teaching about further expansion does not address the question of enrichment; cells can be enriched without expanding them (e.g., by sorting them directly after collection). The instant claims are silent as to excluding embodiments in which cells are expanded prior to administration. Even if the claims did exclude such a step, Strauer's teaching that expanded cells are a non-preferred embodiment would not constitute a teaching away.). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). See M.P.E.P. §2123.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art

may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651